Early Journal Content on JSTOR, Free to Anyone in the World

This article is one of nearly 500,000 scholarly works digitized and made freely available to everyone in the world by JSTOR.

Known as the Early Journal Content, this set of works include research articles, news, letters, and other writings published in more than 200 of the oldest leading academic journals. The works date from the mid-seventeenth to the early twentieth centuries.

We encourage people to read and share the Early Journal Content openly and to tell others that this resource exists. People may post this content online or redistribute in any way for non-commercial purposes.

Read more about Early Journal Content at http://about.jstor.org/participate-jstor/individuals/early-journal-content.

JSTOR is a digital library of academic journals, books, and primary source objects. JSTOR helps people discover, use, and build upon a wide range of content through a powerful research and teaching platform, and preserves this content for future generations. JSTOR is part of ITHAKA, a not-for-profit organization that also includes Ithaka S+R and Portico. For more information about JSTOR, please contact support@jstor.org.

PUBLIC HEALTH REPORTS

VOL. 33 APRIL 26, 1918 No. 17

THE PRESENT STATUS OF OUR KNOWLEDGE OF FATIGUE PRODUCTS.[1]

By ERNEST L. SCOTT, Associate in Physiology, Columbia University; Member of Committee on Industrial Fatigue, Advisory Commission of the Council of National Defense; Physiological Chemist (Scientific Assistant) to the United States Public Health Service.

In 1865 Johannes Ranke (1), then lecturer in the Physiological Institute at Munich, published a book of nearly 500 pages in which he gave the results which he had obtained from his studies on the physiology of muscle. In many ways this book has never been superseded. Among other things he here developed the idea of fatigue substances. At that time Ranke brought out the fact that fatigue is due, at least to a great extent, to something which arises within the organ rather than to the absence of anything used up by the process of muscular contraction. That is, fatigue is to be explained on the basis of a full ash pit rather than an empty coal bin. His principal evidence consisted of the fact that when a fatigued muscle was irrigated with an indifferent fluid, as salt solution, it resumed its power of contraction. Now, it was argued, since the irrigating fluid could not have supplied anything necessary to the muscle, it must have removed something detrimental to it. The substances supposed to have been removed are the fatigue substances.

Obviously, the next point is their isolation and identification. Their identification has been attempted both by chemical comparison of fatigued material with resting material and by the injection into the nonfatigued preparation of substances which are suspected of being fatigue substances. Though the results so far at hand are somewhat disappointing, we have some definite data upon which to base our conclusions.

One of Ranke's experiments consisted in treating a muscle with lactic acid, and by this treatment he obtained fatigue phenomena. Lactic acid was therefore placed in the list of fatigue substances, and has been maintained there. So far as lactic acid is concerned we have progressed considerably beyond the point where Ranke left us.

---

[1] Read before the Section on Industrial Hygiene of the American Public Health Association, Washington, D. C., Oct. 19, 1917.

About 10 years ago Fletcher and Hopkins (2) published a very important paper on the origin of lactic acid in muscle. Though there are some rather discouraging difficulties in the analytical technic which have never been satisfactorily removed, the work reported by these authors leaves no doubt that there is an accumulation of lactic acid or of its salts in excised muscle during fatigue. They further show that the accumulation of lactic acid results from an insufficient supply of oxygen, and that an abundant supply of oxygen prevents the accumulation of the lactic acid or causes its removal in case it has already accumulated. Fletcher and Hopkins have summarized their work in a recent Croonian Lecture (3). At about the time of the appearance of the first paper by Fletcher and Hopkins two articles appeared by Lee (4, 5), in which he gives a very convincing series of tracings obtained from muscles which had been irrigated with solutions containing lactic acid or its salts. These tracings show not only that the onset of fatigue is hastened and that its results are intensified by the presence of lactic acid, but that the familiar phenomenon of treppe, which up to that time had been without satisfactory explanation, was caused by the same substance. Thus treppe, or the augmentation of the contractions which occurs in the early stages of a series, is due to the same material which later causes exhaustion. In a sense it may be considered as the first indication of fatigue. Lee calls attention to the apparent conflict between this fact and the general biological law that metabolic products are harmful to the protoplasm in which they are formed. This conflict is apparent rather than real, for we are in all probability dealing with at least two phenomena, the rate of activity of one of which may be reduced while that of the other may at the same time be augmented. One of these phenomena is the production of lactic acid; another is the effect of this acid, or possibly more accurately of its hydrogen ion, upon the contractile mechanism. The law, in all probability, is, in part, a special application of the more general chemical law of mass action, and if sufficiently accurate methods were at hand it could probably be demonstrated that the rate of formation of the acid is progressively decreased during activity. This is, however, quite apart from the effect of the acid upon the muscle fibers. The activity of these may be augmented or depressed according to the concentration of the acid.

Some years after the articles by Lee appeared, Burridge (6) published the results of a similar set of experiments. While the experiments of Burridge differed somewhat in detail from those of Lee the essential principles involved were the same and the results of the two experimenters agreed. In addition to lactic acid both authors perfused muscle with salts of lactic acid; notably with the lactates of sodium, potassium, and ammonium. Lee found that the salts produced effects similar to those produced by the acid, though perhaps in a somewhat less marked degree, and concluded that both the positive and negative ions were functional in producing fatigue. Burridge worked with the advantage of the beautiful work of Mines (7) before him. A comparison of his results with those of Mines led him to believe that the effects were wholly those of the positive ions. This phase of the problem is distinctly in need of more work.

Since the hydrogen ion seems to be of much importance, one would expect other metabolic products which increase the concentration of this ion to be effective producers of fatigue. In line with this idea, Lee gives records, obtained after treatment of the muscles with carbon dioxide or with potassium dihydrogen phosphate, which show results very similar to those obtained after treatment with lactic acid.

The question of the effect of the negative ion of acids other than lactic arises at this time. Other organic acids may be eliminated in a group from further discussion by the simple statement that normally they are present in very small amounts, if present at all, and that not enough is known concerning them to warrant any discussion at this time. Lee (19) does, however, find that when muscles are perfused with β oxy-butyric acid and its salts, results are obtained which are similar to those given by lactic acid. A study of the effect of the acids derived from glucose and of the fatty acids in their relation to fatigue would be highly interesting and might throw some valuable light on the course of events in intermediate metabolism.

Among the inorganic acids it may be said that no chlorine ion is formed during fatigue because all the chlorine of the body is, so far as we know, present only in the ionic form. There is, however, some modification in the chlorine metabolism. Thus Tissiè (8) found in a 24-hour bicycle race by a professional cyclist that the urinary chlorine output was slightly below normal on the day of work and markedly so on the following day. Harper and Holliday (9) also noted the same reduction in chloride output. This is, however, closely bound up with the chlorine excreted in the perspiration, as shown by Viale (10), who measured the chlorine output per square centimeter of skin area as taken on the foreheads of marching soldiers. He found that the perspiration averaged 0.85 per cent chlorine, but that while the rate of water excretion diminished with the progress of the march that of chlorine increased. So far as I know, there are no figures showing whether or not there is a change of the chlorine relationships in any organ of the body during fatigue. I do not think we are warranted at present in believing that hydrochloric acid or any of its salts stands in any causal relation to fatigue.

Of the other inorganic acids the increased concentration of carbon dioxide is best substantiated. That the concentration of this acid is of great importance is made evident by the very abundant literature on the subject. However, I am not clear as to what extent this substance is effective apart from its rôle as a modifier of hydrogen ion concentration.

Tissiè on his bicyclist and Garratt on himself, as a bicyclist, both observed an increase in the output of phosphates and sulphates in the urine after work. Their experiments were conducted under more or less severe conditions, but I think I am warranted in saying that a man doing ordinary work to which he is daily accustomed secretes somewhat more sulphate at night than he does in the morning. The sulphur, it seems to me, is derived from broken-down protein and may be related to the fact noted by Lee, Scott, and Colvin (11) that muscles capable of doing more severe work contain more protein sulphur. The phosphorous output is thought by most observers to represent a disintegration of the nucleins. Dunlop (16) and co-authors find that the increased phosphorous excretion takes place only in untrained men, though one would hardly expect Tissiè's professional bicyclist to be an untrained man. Here, again, very little is known as to whether phosphoric and sulphuric acids have any effect except that of their hydrogen ion or that resulting from the sweeping of alkalies and alkaline earths from the body.

Many organic extractives have been named as fatigue substances, but the claims for very few, if indeed any, bear careful analysis. One of the earliest of these to be proposed was creatin. This was one of the original list proposed by Ranke, though later he failed to confirm his earlier experiments, and consequently it does not appear in his later lists. Folin's colorometric method for creatinine gave a great impulse to the study of creatin and creatinine and has resulted in a very extensive bibliography on this subject. Among these papers there are several having to do with creatinine or creatin after fatigue. These papers, however, taken as a whole, only add to the confusion, for while Scaffidi (12) and some others report no change in the amount of either creatin or creatinine, Gregor (13) reports a decreased urinary output, while Oddi and Tarulli (14) and others report increases in the amount present in either the muscle or urine after fatigue. Work in our own laboratory indicates clearly that the amount of creatin or of creatinine in muscle is independent of the work done, and this whether the muscle is worked in situ or whether it is excised.

The evidence in regard to uric acid is also more or less conflicting. Judging from what has been said as to the increased output of phosphoric acid and the supposed origin of this acid from the nucleins, one would expect some additional evidence of nuclein metabolism. An increased output of uric acid would be the most probable change.

Tissiè found in the urine of his cyclist on the day of the race about double the amount of uric acid that Folin (15) gives as the average of his 30 normal urines, while on the following day there was a still greater rise. Garratt, again using himself as subject, finds that a slight increase is usual after work, but that in one case, when out of training, the increase was more marked. Dunlop (16) and coauthors think there is no rise when the subject is in training, but otherwise there is an increased excretion of uric acid. They interpret the rise to mean a destruction of protein outside the muscles and suggest that it may be due to a mobilization of the protein of the more inactive portions of the body somewhat akin to the mobilization which takes place during starvation. In their interpretation Garratt agrees with them. Bearing on purine metabolism, attention should be called to the work in which Scaffidi (17) showed that there was no accumulation of uric acid in excised muscles which had been exhausted by fatigue, though there was a loss of fixed purine base. This hardly bears out Dunlop's contention, but on the other hand indicates that the source of the uric acid is the working muscle itself and that perhaps the trained muscle differs from the untrained in its power of breaking up the uric acid, or in the path taken in the disintegration of the purine.

Of course there are numerous other disintegration products which might be expected to arise, as by-products of the working muscle, but evidence that such exist or that they have any bearing on fatigue is even poorer than is that for creatin and uric acid. There is even some question as to whether any protein is destroyed during muscular activity. However, in spite of the fact that according to Luciani (18) Succi excreted no more nitrogen on the twelfth day of his fast when he took exercise than on the eleventh, which he spent in bed, and in spite of the fact that Benedict and Cathcart's (20) experiments indicate no change of urinary nitrogen during work, I feel warranted in believing that there is a definite, though perhaps limited, increased nitrogen output resulting from increased muscular work. Tissiè, again working on the urine of his bicycle rider, reports a normal nitrogen excretion on the day of the race, while on the following day there was an increase of 85 per cent. Garratt agrees with Tissiè in finding no increase during the actual work period, and finds a distinct rise beginning at once after the cessation of work and reaching a maximum some 12 hours later. The excretion did not return to normal for some 30 hours after the work had ceased. This rise followed a different curve from that which followed the taking of food and in addition it occurred during the abstinence from food. Again, Frentzel (21) gives similar results following work done by fasting dogs.

The destruction of protein suggests the possibility that certain of the protein disintegration products may have some bearing upon fatigue. Lee (19) has performed perfusion experiments with indol, skatol, methyl mercaptan, and phenol. In every case he obtained results similar to those obtained with lactic acid or carbon dioxide. These effects were noted in some cases with very small concentrations. There is a general idea extant that the fatigued organism works to less advantage in many ways than does the nonfatigued organism. Normally, the toxic property of such substances as those named is reduced or destroyed by the union of the toxic body with an acid, as sulphuric or gluceronic acid. We are now conducting a series of experiments in the Public Health Service by means of which we hope to show not only whether the output of these bodies is increased during the work day, but also whether the organism can as effectually de-toxify them after as it can before a period of work.

If the destruction of protein is granted, one might expect specific protein toxins which could truthfully be called fatigue toxins, which would be comparable to the bacterial toxins. Such Weichardt (22) claimed to have found and named "kinitoxin." This he originally prepared from the muscle of fatigued animals and when it was injected into the blood streams of normal animals it was reported to produce the phenomena of fatigue. Weichardt himself soon abandoned his original line of research and became interested in some bizarre experiments which apparently led to nothing of present interest. Other workers have found it difficult or impossible to repeat his work, and finally Korff-Peterson (23) and Lee and Aronovitch (24) conclude definitely that no such bodies result in the course of normal fatigue.

To summarize, we may conclude that—

1. Substances carrying hydrogen ions, as lactic, β oxy-butyric acids, potassium, dihydrogen phosphate and carbon dioxide, stand as causal agents of fatigue.
2. Certain products of protein disintegration, as indol, skatol and phenol may produce fatigue symptoms and may be active agents in producing normal fatigue.
3. There is some evidence that the negative ion of lactic and β oxy-butyric acids and that certain positive ions, especially that of potassium, are capable of producing certain fatigue phenomena.
4. There is no evidence that the negative ions of carbonic, phosphoric or sulphuric acids are fatigue substances.
5. There is no evidence at present for the existence of specific fatigue substances as proposed by Weichardt.
6. There is very little probability that creatin or creatinine have any relation to fatigue or to muscle work in general.
7. There are no doubt numerous bodies, as purine bases, uric acid, etc., which may be increased by work, but which have no causal bearing on fatigue.

Literature Referred to.

(1) Ranke, Tetanus, book, Leipzig, 1865.

(2) Fletcher and Hopkins, Lactic Acid in Amphibian Muscle, Journal of Physiology, 1904, XXX, 414.

(3) Croonian Lecture: The respiratory Process in Muscle and the Nature of Muscular Motion, Proceed. Roy. Soc., B. 1917, LXXXIX, 444.

(4) Lee, The Cause of Treppe, Am. Journ. Physiol., 1907, XVIII, 267.

(5) The Normal Action of Fatigue Substances on Muscle, Am. Journ. Physiol., 1907, XX, 170.

(6) Burridge, An Inquiry into some Chemical Factors of Fatigue, Journ. Physiol., 1910, XLI, 285.

(7) Mines, On the Spontaneous Movements of Amphibian Skeletal Muscle in Saline Solutions. Journ. Physiol., 1908, XXXVII, 408.

(8) Tissiè, Observations Physiologiques concernant un Record Vélocipédique., Arch. de Physiol., 1894, VI, 822.

(9) Harper and Holliday, A Contribution to the Chemistry of Fatigue. Journ. Am. Chem. Soci., 1903, XXV, 33.

(10) Viale, The Excretion of Sodium Chloride in the Perspiration During Fatigue. Atti accad. Lincei., 1913, XXII, 180.

(11) Lee, Scott and Colvin, Some of the Chemical Characters of Certain Mammalian Muscles. Am. Journ. Physiol., 1916, XL, 474.

(12) Scaffidi, Sur la présence de créatinine dans les muscles et sur le mode de comporter de la créatine durant la fatigue. Arch. Ital. Biol., 1914, LXI, 168.

(13) Gregor, Beiträge zur Physiolog. des Kreatinins. Ztsch. Physiol. Chem., 1900, XXI, 98.

(14) Oddi and Tarulli, Bul. del' Accad. Med. di Roma, 1893, XIX, 57.

(15) Folin, Approximately complete analyses of thirty normal urines, Am. Journ. Physiol., 1905, XIII, 45.

(16) Dunlop and others, Muscular Exercises and Metabolism, Journ. Physiol., 1897, XXII, 68.

(17) Scaffidi, Ueber das Verhalten der Purinebasen der Muskeln während Arbeit, Biochem. Ztsch., 1911, XXX, 473.

(18) Luciani, Das Hungern, p. 123, book, 1900.

(19) Lee, The Causes of Fatigue in Certain Pathological States, Brit. Med. Journ., 1906, II, 1806.

(20) Benedict and Cathcart, Muscular Work. Carnegie Pub., 1913, p. 98.

(21) Frentzel, Ein Beitrag zur Frage nach der Quelle der Muskelkraft, Pfluger's Archive, 1897, LXVIII, 212.

(22) Weichardt, Ueber Ermüdungsstoffe, book, 1912.

(23) Korff-Peterson, Untersuchungen über Kenotoxin. Ztsch. Hyg., 1914, LXXVIII, 37.

(24) Lee and Aronovitch, Does a Fatigue Toxin Exist? Proc. Soc. Exp. Biol. and Med., 1917, XIV, 153.

Additional literature will be found in the article on fatigue by Ioteyko in Richet's Dictionaire de Physiologie, Vol. 6, 1904.